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Optimizing care for patients with symptomatic carotid disease

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CHAPTER 3

Endarterectomy or carotid artery
stenting: the quest continues
part two

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ABSTRACT

Background. Although randomized trials on carotid artery stenting (CAS) could not establish its equivalence to carotid endarterectomy (CEA) in patients with symptomatic carotid disease, CAS is rapidly evolving. Data on long-term outcome after CAS from randomized trials have now become available and ongoing, prospectively held registries frequently publish their results in increasing numbers of patients. We have therefore reviewed the currently available literature and provide an update of our previous article on this topic.

Data sources. PubMed literature searches were performed to identify relevant studies regarding current status of carotid endarterectomy and stenting for symptomatic carotid stenosis.

Conclusions. The efficacy of CAS in patients with symptomatic carotid artery stenosis remains unclear due to varying results in randomized trials. Although multiple registries do report promising results after CAS, peri-interventional stroke/ death rates still exceed those rates currently found after CEA. Therefore, CEA remains the ‘gold standard’ in treating these patients.

INTRODUCTION

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ESCT) demonstrated that best medical treatment (BMT) combined with carotid endarterectomy (CEA) reduce the absolute risk of developing severe stroke or death in patients with symptomatic severe or moderate stenosis.^{1,2} Current guidelines in how to treat these patients best are still based on these studies, which have been published almost two decades ago. Since then, many developments have taken place in the era of stroke prevention. The recognition of the importance of life-style adjustments and BMT has grown tremendously, reflected by national programs to discourage tobacco use worldwide and the growing use of statins to become standard care in all patients with vascular disease nowadays. Furthermore, percutaneous transluminal carotid angioplasty and stenting (CAS) has made its entrance into the field of treating patients with carotid stenosis and has already been studied widely as an alternative to CEA. CAS is less invasive compared to CEA and has a decreased risk for cranial nerve damage as well as the ability to treat lesions that are beyond the reach of CEA. However, early trials were not able to demonstrate superiority or non-inferiority of CAS with respect to 30-day stroke rate and/or death in symptomatic patients and CEA still remained ‘gold standard’ for treatment.³⁻⁷

In 2008, our group published a review describing the early literature regarding CAS in this journal.⁸ Meanwhile, ongoing surveillance studies demonstrate that increase in operator experience and better patient selection translate into improved results after CAS.⁹ Furthermore, long-term results of the early CAS trials have been published and more studies have been published on the value of CAS in real-world patients. In some guidelines, CAS has even already been proposed as an alternative to CEA in symptomatic patients and highly selected asymptomatic patients.¹⁰ We have therefore reviewed the currently available literature on this topic and provide an update in this subsequent article.

Randomized controlled trials comparing CAS and CEA

Several randomized controlled trials have been performed to establish the validity of endovascular treatment as an alternative to CEA in patients with symptomatic carotid stenosis. Because of the limitations of several early prospective studies, such as the inclusion of predominantly asymptomatic patients or the performance of angioplasty without stenting, and the substantial larger amounts of patients in the more recent studies, we will mainly discuss the following trials in this paper: ‘Stenting in patients with symptomatic severe carotid stenosis’ (EVA-3S), the ‘Stent protected angioplasty versus carotid endarterectomy’ (SPACE) study, the ‘International carotid stenting study’ (ICSS), and the ‘Carotid revascularization endarterectomy vs. stenting trial’ (CREST).^{5,7,11,12} The characteristics of these studies are provided in table 1 and the short-term and long-term results in table 2 and 3.

We already discussed the short-term results of EVA-3S and SPACE in our earlier report.⁸ In short, both were European non-inferiority studies including symptomatic patients. Interim analysis in EVA-3S showed a significant higher risk for death or any stroke at 30 days for CAS (9.6%) compared to CEA (3.9%). For reasons of both safety and futility EVA-3S was terminated early, leaving the inferiority question unanswered.⁵ In contrast, in SPACE, the risk for severe ipsilateral stroke or death between randomization and 30 days after treatment was comparable in patients treated by CAS and patients treated by CEA (6.8% versus 6.3%, respectively). However non-inferiority of CAS could not be demonstrated.⁷

The cumulative risks of peri-procedural stroke or death and non-procedural ipsilateral stroke after four years follow-up in the enrolled patients in EVA-3S remained significantly higher in patients who had undergone CAS (11.1% versus 6.2% after CEA). This was mainly caused by to the poor 30-day results: the risk of ipsilateral stroke beyond the peri-procedural period was low and similar in both groups.¹³ Long-term outcome in SPACE after two years follow-up was similar for both treatments: in the post-procedural period the ipsilateral stroke rate was 2.2% for the stenting group versus 1.9% in the CEA group.¹⁴

In 2010 the short-term results of ICSS were published.¹² Interim analysis after 120 days showed a higher 30-day incidence of any stroke, myocardial infarction (MI) or death in the CAS-group compared to the CEA-group (table 2). Non-disabling stroke as well as fatal stroke occurred more often in the CAS-group (4.6% vs. 1.6% and 1.1% vs. 0.2%, respectively). Because the number of non-disabling strokes could be underestimated in the CEA-group due to the use of general anaesthesia, a substudy of the ICSS was performed to investigate the rate of ischemic brain injury detectable on MRI one day after treatment. About three times more patients in the stenting group had new ischemic lesions on post-treatment scans compared to patients in the endarterectomy group. Interestingly, cerebral protection devices (CPD's) did not seem to be effective in preventing cerebral ischemia during stenting.¹⁵

Table 1. Characteristics of four prospective randomized trials focusing on early and late outcome of carotid endarterectomy or carotid artery stenting in patients with symptomatic carotid stenosis.

Study	Patients		Primary Outcome
	n	Percentage with symptomatic stenosis	
EVA-3S ⁵	527	100	Composite of any stroke or death occurring within 30 days after treatment
SPACE ⁷	1200	100	Ipsilateral stroke or death of any cause between randomization and 30 days after treatment
ICSS ¹²	1713	100	Fatal or disabling stroke in any territory within 3 years after procedure
CREST ¹⁰	2502	52	Composite of any stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization

CREST, carotid revascularization endarterectomy versus stenting trial; *EVA-3S*, stenting in patients with symptomatic severe carotid stenosis; *ICSS*, international carotid stenting study; *SPACE*, stent protected angioplasty versus carotid endarterectomy.

EVA-3S, SPACE and ICSS could thus not establish equivalence of CAS in terms of validity and safety. Their separate results did however suggest that peri-procedural risks of CAS vary with patient characteristics.¹⁶ This is also known for CEA.¹⁷ Because the three trials were all underpowered to investigate whether CAS might be a safe alternative in specific subgroups, a collaboration was set up early during the design stage of the separate trials.¹⁶ The purpose of this Carotid Stenting Trialist's Collaboration (CSTC) was to perform a meta-analysis of individual patient data from the three trials. Primary outcome event was

any stroke or death. In this pooled analysis, CAS was associated with a significant higher rate of primary outcome events compared to CEA (8.9% vs. 5.8%, p=0.0006). Non-disabling strokes contributed for the largest part of the combined primary outcome event. Of all the predefined subgroup variables, only age seemed to significantly influence the risk of the primary outcome event. Primary outcome event was twice as high after CAS compared to CEA in patients above the age of 70 (12.0% vs. 5.9%; Risk Ratio 2.04) whereas the risks were similar between both treatment groups in patients younger than 70 years of age (5.8 versus 5.7%, Risk Ratio 1.00).

Table 2. Comparison of the outcome of percutaneous transluminal angioplasty with stenting ('CAS') and carotid endarterectomy ('CEA') within 30 days after the procedure in symptomatic patients.

Study	Stroke or death			Stroke, myocardial infarction or death		
	CAS (%)	CEA (%)	RR, OR of HR (95%-CI)	CAS (%)	CEA (%)	RR, OR of HR (95%-CI)
EVA-3S	9.6	3.9	<i>RR 2.5 (1.2-5.1)*</i>	10.0	4.7	<i>RR 2.1 (1.0-4.9)*</i>
SPACE	6.9	6.4	OR 1.1 (0.7-1.7)	6.9	6.4	OR 1.1 (0.7-1.7)
ICSS	7.4	3.4	<i>RR 2.2 (1.4-3.3)*</i>	7.4	4.0	<i>RR 1.8 (1.2-2.8)*</i>
CREST	6.0	3.2	<i>HR 1.9 (1.1-3.2)*</i>	6.7	5.4	HR 1.3 (0.8-2.0)

Italicized figures indicate statistical significant difference in outcome. *CAS*, carotid artery stenting; *CEA*, carotid endarterectomy; *CI*, confidence interval; *CREST*, carotid revascularization endarterectomy versus stenting trial; *EVA-3S*, stenting in patients with symptomatic severe carotid stenosis; *HR*, hazard ratio; *ICSS*, international carotid stenting study; *OR*, odds ratio; *RR*, risk ratio; *SPACE*, stent protected angioplasty versus carotid endarterectomy.
*p < 0.05 for significant difference in outcome after CAS versus CEA

The latest and largest randomized trial designed to evaluate CAS, CREST, differed somewhat from the other trials.¹¹ First, CREST was initially designed to assess the efficacy of CEA and CAS in patients with symptomatic carotid stenosis. However, after benefit for CEA had been reported in the Asymptomatic Carotid Surgery Trial (ACST), asymptomatic patients were also enrolled in the trial.^{18,19} Furthermore, because the European trials were criticized for limited requirements for endovascular experience, CREST was designed to account for a learning curve associated with carotid stenting. Before participation in the study, interventionalists underwent a comprehensive and rigorous credentialing process that included a careful selection, training in CREST-study devices and a lead-in phase, in which they had to perform a number of procedures based on their previous experience.²⁰

Analysis among symptomatic patients in CREST (n=1321) revealed no significant difference in the composite endpoint of stroke, myocardial infarction (MI) or death between CAS and CEA (6.7% vs. 5.4%, respectively). However, the risk for developing stroke was significantly higher in the CAS-group (5.5% vs. 3.2% after CEA, P=0.04).¹¹ Although this difference disappeared during follow-up (table 3), peri-procedural stroke has been independently associated with a nearly threefold increase in future mortality.²¹

A recent meta-analysis by the Cochrane Collaboration of eleven randomized trials, comparing endovascular treatment with CEA in symptomatic patients demonstrated that endovascular treatment

was associated with a higher stroke and death rate between randomization and 30 days after treatment (Odds ratio (OR) 1.72, 95% confidence interval (CI): 1.29 - 2.31, P= 0.0003).²² This meta-analysis however included studies that might be less relevant because of the use of outdated techniques or performing angioplasty without stent placement. Another recent meta-analysis of thirteen randomized trials showed similar results.²³ This publication however included a second analysis, which was restricted to the two most recent trials with the better methodology and more contemporary technique (ICSS and CREST).²³ Again, CAS showed to be associated with a significant increase in the risk of any stroke (RR, 1.82; 95% CI, 1.35-2.45) and mortality (RR, 2.53; 95% CI, 1.27-5.08).²³

The results of these four trials indicate that CEA is still the treatment of choice in patients with symptomatic carotid disease. We do however have to consider several issues when interpreting and comparing the results of the trials.

Experience

First, limited experience in endovascular treatment of carotid stenosis remains topic of debate. In EVA-3S, “sufficient technical expertise” was defined as having performed 12 carotid stenting procedures or 35 supra-aortic endovascular procedures ever. If the specialist was not able to meet these criteria the procedure had to be performed under supervision.⁵ In SPACE, interventionalists had to show proof of at least 25 successful consecutive percutaneous transluminal angioplasty or stent procedures and in ICSS a minimum of 50 stenting procedures was required for qualification, of which at least 10 were performed in the carotid artery.^{7,12} In ICSS, centers not fulfilling these criteria had to be proctored by an external interventionalist. In CREST interventionalists and surgeons were only allowed to participate after comprehensive external evaluation of their results (“lead-in phase”) as described above. This might explain the lower risk of death and stroke in the first 30 days after stenting in CREST compared to EVA-3S. However, the risk in CREST only differs marginally from the results in SPACE and ICSS (table 2). Moreover, little or no difference in results after CAS was observed between interventionalists with much or less experience in EVA-3S and ICSS. In EVA-3S, risk of patient death or stroke 30 days after CAS was 12.2% for clinicians who have had performed more than 50 stent procedures in the past compared to 11.0% for those with less than 50 procedures, and 7.1% for those performing the procedure under supervision (P= 0.49).²⁴ A significant difference in primary outcome after CAS between experienced and supervised centers was neither found in ICSS (8.7% vs. 6.9%, P= 0.444).¹² On the contrary, results of several large prospective multicenter registries (discussed hereafter) do show declining death/stroke rates with increasing interventionalists and centers experience, with rates even lower than in CREST.²⁵⁻²⁷ This better outcome in the more recently treated patients in the registries, might be influenced by the increasing awareness that treatment should not be delayed.²⁸ Other potential biases that could have caused different outcomes in different trials include variations in peri-procedural medical management and degree of stenosis. Thus, although a learning curve for CAS is expected and a relation between experience and outcome is seen in prospective registries, this was not supported by subgroup analyses of the randomized trials. Moreover, despite ‘highly’ experienced interventionalists, the peri-operative outcome still favored CEA in CREST.

Table 3. Long-term results of CAS versus CEA in symptomatic patients.

Study	Follow-up in years	Outcome measure	Patients with unfavourable outcome (%)		Hazard ratio (95%-CI)
			CAS	CEA	
EVA-3S	4	death or stroke within 30 days after intervention or ipsilateral stroke during follow-up	11.1	6.2	2.0 (1.1-3.7)*
SPACE	2	death or stroke within 30 days after intervention or ischemic stroke during follow-up	9.5	8.8	1.1 (0.8-1.6)
ICSS†	0.3	death, stroke or myocardial infarction during follow-up	8.5	5.2	1.7(1.2-2.5)*
CREST‡	4	death or stroke within 30 days after intervention or ipsilateral stroke during follow-up	8.0	6.4	1.4(0.9-2.1)

Italicized figures indicate statistical significance.
*p < 0.05 for the difference in outcome of CAS compared to CEA
†Interim analysis of the results up to 120 days after randomization (intention-to-treat-analysis); the final follow-up takes 3 years; the outcome measure for long-term results will be stroke during follow up (see table 1)
‡Interim analysis.

Primary outcome

Since MI might be expected to occur more often after CEA compared to CAS, it was included in the primary and secondary outcomes in three of the four trials. Although this has indeed been demonstrated in meta-analyses, only few peri-procedural myocardial infarctions were actually recorded in the trials: none in SPACE, 1 versus 2 for respectively CAS and CEA in EVA-3S, 3 versus 5 in ICSS and 14 versus 28 in CREST.^{22,23} Thus, most myocardial infarctions were seen in CREST, but MI was broadly defined as an increase in troponin concentration twice or more the upper reference value or ECG abnormalities suggestive of myocardial ischemia, including ST-segment depression. It is therefore unclear whether it concerned patients with a true MI or patients with only a transient period of myocardial ischemia. On the other hand, any stroke between randomization and 30 days after treatment was far more often seen in all the studies.²² CREST itself demonstrated that both disabling as non-disabling stroke are associated with a marked decrease in quality of life one year after the intervention, whereas the effect of peri-procedural MI was less certain.¹¹ Besides symptomatic stroke, interventions on carotid arteries can also be accompanied by silent strokes without any deficit of focal neurological function. Patients undergoing stenting are three times more likely to have new intracerebral lesions on MRI after intervention than patients after CEA.¹⁵ The occurrence of a silent stroke is related to cognitive impairment and possibly to the development of vascular dementia.²⁹

So do the small numbers of peri-procedural ischemic cardiac events weigh up against the larger numbers of ischemic cerebrovascular events? If they do at all, their impact on the outcome for the individual patient is probably much smaller. The logical next question is then whether MI should be included in the primary end-point in studies comparing CAS and CEA. After all, the purpose of carotid intervention in symptomatic patients is secondary stroke prevention and with that, disability and death.

Revisiting the outcome of symptomatic patients in CREST after excluding MI from the primary outcome fairly changes the primary conclusion drawn by the authors (table2).

Asymptomatic patients

Another point of interest when comparing the trials is the heterogeneity of the patients included. All patients in EVA-3S, SPACE and ICSS were symptomatic. However, half of all patients included in CREST had no prior neurological event. In SAPHIRE, which will be discussed hereafter, even 71% of all patients were asymptomatic. The use of CAS in treating carotid stenosis has been endorsed by guidelines using evidence of predominantly these two trials.¹⁰ Although ACAS and ACST-1 demonstrated the value of CEA in asymptomatic patients, numbers needed to treat were rather high.^{30,31} Whether or not to treat these patients surgically is therefore still fiercely debated. Moreover, primary prevention has improved tremendously the last decade, resulting in reduced risk of stroke in asymptomatic patients.³² Again, the conclusions drawn from CREST must be seen in this perspective. Perhaps SPACE-2, a currently recruiting three-arm clinical trial to investigate the superiority of CAS and CEA compared to best medical treatment alone in asymptomatic patients, and in case superiority has been demonstrated, to investigate whether CAS is not inferior to CEA, will provide some enlightenment on this matter.³³

Age

There are strong indications that age at the time of intervention has its effects on the outcome. In both CREST and the pooled analysis of the European trials, risk for stroke or death was significantly higher after CAS compared to CEA in patients beyond the age of 70. Moreover, in these patients, risk ratios continued to increase with age at the expense of CAS.^{11,16} On the contrary, CEA has been shown safe and effective in patients above the age of 80.³⁴ In CSTC, the outcome after CAS and CEA in symptomatic patients younger than 70 years seemed to be equal, although the 95% coincidence interval was wide (risk ratio 1.00; 95% CI 0.68-1.47).¹⁶ Probably, some of these patients benefit from CEA, others seems to be better off with CAS. The finding of an increased stroke risk after CAS compared to CEA in the older (symptomatic) patient is supported by the outcome in several large registries.³⁵⁻³⁷ Recent data from the Society for Vascular Surgery Vascular Registry (SVS-VR, n= 8913) show that CAS is associated with inferior 30-day outcomes in both symptomatic as asymptomatic patients aged ≥ 65 years. The 30-day death/ stroke/ MI rate in symptomatic patients ≥ 65 years was 9.5% after CAS compared to 6.0 % after CEA (p= 0.0007). In patients younger than 65 years there were no significant differences in mortality, stroke or MI.³⁶ An earlier report from the German prospective CAS registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK) shows a 30-day death/ stroke rate of 7.1% in symptomatic octogenarians.³⁷

Although the available evidence is based on subgroup analyses and non randomized studies, and therefore care must be taken when using age as guidance in case selection, one can fairly state that CAS should not be offered to the older symptomatic patients.

Cerebral protection devices

The use of cerebral protection devices (CPD's) in CAS is another matter of continuous debate. A recent European guideline states that CPD's are probably beneficial in CAS, although this was not supported by level A evidence.³⁸ The systematic use of CPD's was recommended in EVA-3S after an interim analysis showed a higher stroke-risk in patients treated without.³⁹ Eventually, CPD's were used in 91.9% of all

patients treated with CAS. In SPACE the use of a CPD was left to the discretion of the interventionalist and was used in 27%.⁷ ICSS recommended the use whenever feasible (in 78% of all CAS-patients) and in CREST the use of a CPD was mandatory (used in 96.1%).^{11,12} Subgroup-analysis in SPACE and ICSS showed however no additional value for the use of CPD's.^{7,15}

Table 4. Recent studies on the outcome of CAS using CPD's

Study (year of publication)	n (% symptomatic)	Type of protection device (proximal vs distal)	% overall 30-day outcome (death/ stroke/ MI)	% 30-day death/ stroke in symptomatic patients
Loghmanpour <i>et al</i> (2013) ⁵⁵	731 (41)	distal	8.3 *	9/ 4.7 **
Matsumura <i>et al</i> (2012) ⁴⁵ †‡	220 (12.8)	distal	2.3	n/a
Nikas <i>et al</i> (2012) ⁴⁷ ‡	122 (28.8)	proximal	1.6 ***	0.0
Stabile <i>et al</i> (2012) ⁶⁴	441 (27.4)	both	1.37 ***	2.0
Myla <i>et al</i> (2010) ⁴⁶ †‡	237 (20.3)	distal	3.0	4.2
Ansel <i>et al</i> (2010) ⁴⁰ †‡	262 (15.1)	proximal	3.0	0.0
Stabile <i>et al</i> (2010) ⁴⁸ †	1300 (27.8)	proximal	1.4 ***	3.0
Clair <i>et al</i> (2010) ⁴¹ ‡	245 (31.8)	proximal	3.7	2.6
Matsumura <i>et al</i> (2010) ⁴⁴ †	5297 (14.3)	distal	2.7 ****	4.6 ****
Gray <i>et al</i> (2009) ⁹ †∞	6320 (12.0)	distal	3.6 ***	6.4
Higashida <i>et al</i> (2009) ⁷⁰ †	498 (42.9)	distal	5.4	8.4 *****
Massop <i>et al</i> (2008) ⁴³ †	2001 (27.7)	distal	4.4	n/a
Katzen <i>et al</i> (2007) ⁴²	1493 (21.8)	distal	5.0	5.3/0.9**
* includes TIA				
** stroke/ death rate respectively				
*** death/stroke				
**** stroke				
***** includes MI				
† commercially funded/ conflict of interest reported				
‡ exclusion of symptomatic patients with stroke 14-30 days prior to intervention				
∞ interim data CAPTURE 2 and final results EXACT study combined				
n/a not available				

Since the publication of these trials, interventionalist's experience has increased and devices have been improved. Several studies have been published recently addressing the use of CPD's in CAS (table 4). The majority of these studies are postmarket studies to assess the efficacy and safety of the approved devices.^{9,40-48} Most of the included patients in these studies are however asymptomatic (table 4). The 30-day death/stroke rates in symptomatic patients vary between 0 and 6.4% (table 4), but many of these studies excluded patients who had suffered a stroke 14 to 30 days prior to intervention.^{40,41,45-47} The figures might be higher in real-world patients. Results from an observational study have namely shown a higher risk for a recurrent event during the first weeks after the index event, and subgroup-analysis of the landmark trials on CEA showed that the benefit of an intervention was the highest within the first two weeks after randomization (i.e. approximately within the first three weeks after the index

event).^{17,49} Indeed, analysis of CSTC-data demonstrates that CAS within 14 days after the index event is associated with an increased risk of stroke or death.⁵⁰ Furthermore, the combined 30-day death/stroke rates in symptomatic patients as presented in table 4 are still higher than those found after CEA in EVA-3s, ICSS, CREST and several large recently published registries which included a surgical arm (figure 1).^{5,11,12,51-53}

Another discussion is what type of protection should be used. Three types of protection devices have been developed: distal filters, distal occlusion and proximal occlusion balloons. The various types of devices all have their own advantages and disadvantages.⁵⁴ The major concern of distal protection is the necessity to cross the (vulnerable) carotid stenosis before initiating protection. A recent retrospective study by Loghmanpour on 6 different (distal) filter devices showed fairly high 30-day stroke rates in symptomatic patients compared to the results of postmarket studies on proximal devices (table 4).^{40,41,47,48,55} To our knowledge, only two small randomized trials using surrogate endpoints have been performed comparing proximal and distal protection, demonstrating different results.^{56,57}

Summarizing, although CPD's are generally recommended in CAS nowadays, evidence for either its use, as well as for what type to be used, remains weak.

Real-world patient

In all four trials, numerous in- and exclusion criteria defined the eligibility of the potential participating patients. There were 21 clinical and 7 anatomical exclusion criteria in CREST, 10 exclusion criteria in ICSS, 14 in SPACE and 10 in EVA-3S.^{13,19,58,59} Are patients meeting these exclusion criteria really at risk when undergoing a carotid intervention and can the results of these trials, performed in a selected group of patients, be extrapolated to daily practice?

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial (SAPPHIRE), published prior to the earlier discussed trials, was designed to determine a revascularization strategy for patients with severe carotid artery stenosis and coexisting conditions that would have excluded them from NASCET and ACAS.⁶⁰ These criteria of 'high risk' comprised clinically significant cardiac disease, severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, previous radical neck surgery or radiation therapy to the neck recurrent stenosis after endarterectomy and age >80 years, and were partly in accordance with the exclusion criteria used in CREST and ICSS later on.^{19,58} Patients in which CEA was considered to be unsafe but in which stenting was judged to be feasible entered into a stent registry, and vice versa. The primary end point of the trial was the cumulative incidence of death, stroke, or MI within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. Eventually (the study was terminated early when the enrollment in the trial slowed down after several nonrandomized carotid-stent registries had become available) 747 patients were enrolled in the study of which 344 underwent randomization and 413 entered the registries. The primary end point occurred in 12.2% of those who underwent CAS compared to 20.1% who underwent CEA ($P=0.004$ for noninferiority). A more conventional end point (stroke or death at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 year) occurred however in only 5.1% versus 7.5% respectively ($P=0.40$). Moreover, the majority (71%) of the randomized patients were asymptomatic. Analysis of the symptomatic patients showed a cumulative incidence of the primary end point of 16.8% after CAS compared to 16.5% after CEA ($P=0.95$). After three years,

no significant difference in major secondary end point (composite of death, stroke, or MI within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1080 days) could be shown between CAS and CEA with 41 (24,6%) and 45 (26,9%; $P=0.71$) events respectively (in both symptomatic and asymptomatic patients).⁶¹ Finally, no differences in health status impairment or in health related quality of life were found from one month on after the intervention.⁶²

Also, over 50% of those patients eligible for randomization were excluded from SAPPHIRE because of high operative risks. Without these assumed very high risk patients, primary end point was still quite high in symptomatic patients compared to CREST, which also included MI in its primary end point, in both patients receiving CAS and CEA (table 2). Although CAS showed no inferiority to CEA in the primary end point, CAS seems certainly not to be better in symptomatic patients with presumed higher surgical risk.

Data on results of CAS in daily practice can further be deducted from several published multi-center registries (Figure 1). Interpreting these studies requires some caution because of the variety in background and design. Some of these registries are single arm postmarketing surveillance (PMS) studies, conducted by manufacturers to evaluate the performance of their stents and devices in more real-world circumstances. Other registries are based on data from regional or national vascular databases or databases held by scientific societies, containing either just an endovascular arm, or having a surgical arm as well.^{51-53,63,64}

Most of the PMS studies are conducted in 'high risk' patients since patient selection has to be consistent with the approved device indications for use. Although the 30-day death/stroke rates are promising with only slightly higher outcomes compared to those in 'standard patients' in ICSS and CREST (Table 2; Figure 1) there are some concerns regarding the commercially funded studies. A recent comparison of patient characteristics between PMS study participants and nonparticipants within the NCDR CARE registry (a comprehensive, voluntary, national registry of patients undergoing CAS or CEA), demonstrated that participants in PMS studies for CAS have different clinical and procedural characteristics and lower mortality compared with nonparticipants.⁶⁵ These studies might be subjected to pre-selection since inclusion of patients with unfavorable anatomy as deciding criterion for 'high-risk' (up to 28% in symptomatic patients in CAPTURE 2) could dilute the outcome. The 30-day risk following CAS in patients with non-atherosclerotic disease is known to be much lower than in atherosclerotic disease.^{28,44} The results found in these studies must further not be overestimated since the procedures in these studies are generally performed by very dedicated, experienced interventionalists and post-procedural neurological examination by a neurologist is mostly not imperative. Thus, the outcome of these studies as presented in figure 1 might be worse in daily practice.

Recently, several regional or national registries which did include a surgical arm have been published. In 2012, the Vascular Study Group of New England published the results of a retrospective analysis of all patients undergoing CAS and CEA in their centers from 2003 to 2010, reflecting outcomes in real-world patients. Outcomes were stratified by symptomatic status. Symptomatic patients undergoing CAS ($n=430$) showed higher rates of stroke or death than those who had received CEA ($n=7649$) (5.1% vs 1.6%; $P=0.001$), and also higher stroke, death, or MI rates (5.8% vs 2.7%; $P=0.02$), with predominantly higher stroke rates in CAS (3.8% vs 1.2%, $P=0.004$). There were more patients with coronary artery disease,

congestive heart failure and COPD in the CAS group, however, after accounting for these differences in comorbidity, there was still an increased risk of stroke or death in symptomatic patients undergoing CAS compared with CEA.⁵²

The Society for Vascular Surgery (SVS) has also designed a vascular registry (SVS-VR) to collect real-world data on the outcome after CAS and CEA. The SVS-VR does not have any inclusion or exclusion criteria for patient eligibility. In a recent publication, data collected from 56 centers on 2763 CAS patients and 3259 CEA patients was analyzed.⁵³ At 30 days, the combined death/stroke/MI rate in symptomatic patients was 7.13% for CAS and 3.75% for CEA. After risk-adjustment for age, history of stroke, diabetes, and ASA grade (ie. factors found to be significant confounders in outcomes), outcomes were still better after CEA. Data derived from the National Swedish Registry of Vascular Surgery on symptomatic patients treated with CEA (n= 5435) or CAS (n=253) between 2004 and 2011 show however no differences in 30 day death/stroke rates (4.3% vs 4.0%, respectively). Almost half of the procedures were performed in one single institution. Without the results of this highly experienced center 30-day outcome in death/stroke were 4.4% vs 4.9%, respectively. Furthermore, the total stroke and death rate after all CAS-procedures (including asymptomatic patients) reduced during the period, from 6.4% in 2004-2008 to 3.6% in 2008-2011.⁵¹

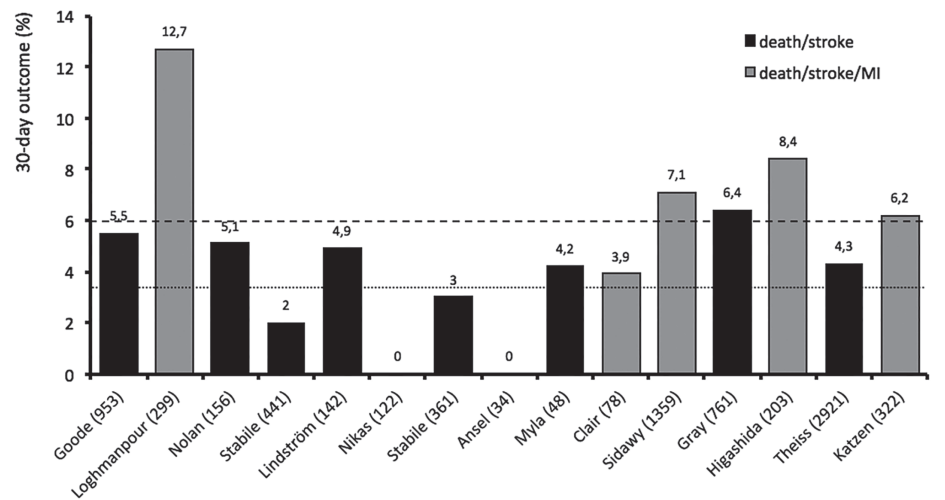


Figure 1. 30-day outcome after CAS in symptomatic patients (numbers between the brackets) in recently published registries and observational studies.^{9,27,40-42,46-48,51-53,55,63,64,70} The dashed line represents the maximum of 6% perioperative morbidity and mortality as recommended by various international guidelines. The dotted line represents the overall outcome after CEA in those registries which include a surgical arm (293 events in 8546 symptomatic patients).⁵¹⁻⁵³

Although these registries show varying outcomes and they might be subjected to selection- and other biases as discussed above, the overall death/ stroke rates after CAS are only slightly higher than those after CEA found in the randomized trials (table 2; figure 1). This does in one way consolidate the results of the randomized controlled trials that CEA is still the treatment of choice in symptomatic patients. On

the other hand, the ‘real-world’ outcomes do lie within the 6% perioperative morbidity and mortality boundary maintained in international guidelines for (surgical) treatment of symptomatic patients with severe carotid stenosis.^{66,67} However, perioperative morbidity and mortality after CEA were considerably lower in EVA-3S, ICSS and CREST than they were in NASCET and ECST, on which the 6% is based (table 2).

Large observational studies therefore do justify the use of CAS in those symptomatic patients in whom surgery is not feasible, provided certain criteria like operator experience and low peri-interventional morbidity and mortality are met. Whether or not surgery is feasible should carefully be considered in each individual patient. A broad concept of the ‘high-risk’ patient based merely on the exclusion criteria of the trials cannot be justified and evidence for individual risk factors that may adversely affect the outcome only comes from institution based studies and case series.⁶⁸

Additional factors

Besides the considerations already discussed, several other factors should be regarded for clear interpretation and comparison of the above discussed randomized trials. Pooled data of NASCET and ECST demonstrated differences in risk reduction by CEA in patients with varying degrees of carotid stenosis. Moreover the risk reduction seemed to be influenced by the timing of surgery. Patients with a carotid stenosis of $\geq 70\%$, treated within 14 days after the most recent event, benefitted intervention most.⁶⁹ In the European carotid stenting trials, symptomatic patients with a stenosis of $\geq 50\%$ were included and only about one quarter of these patients was actually treated within the time-frame of two weeks.¹⁶ These factors might have influenced the outcome of the studies. On the other hand, a recently published study showed that the risk of CAS compared to CEA appears to be greatest in patients treated within 7 days of symptoms, tipping the balance further to CEA in symptomatic patients (death/ stroke rate 9.5% vs 2.8%; RR 3.4; 95CI 1.01-11.8).⁵⁰

EVA-3S and SPACE were terminated early because of the results of preplanned interim-analyses. The number of included patients initially deemed necessary to gain enough power was therefore not met. Different primary outcome measures and different peri-interventional antithrombotic regimes further impede a clear comparison between the trials. Finally, unstable plaques, intraluminal thrombi, a tortuous carotid artery or an abnormal aortic arch might make the patient a poor candidate for CAS. However, these anatomical and morphological characteristics have hardly been studied yet.

In conclusion, long-term results after CAS in symptomatic patients differ between the randomized trials. There is however no tendency towards favoring CAS. Interpreting the combined long-term results is hampered by variation in patient selection, primary outcome and several other factors. Death and stroke rates in ongoing CAS registries are promising, but are still higher than those found after CEA and must be interpreted with caution. Therefore, CEA remains the ‘gold-standard’ for treatment of patients with symptomatic carotid stenosis. In those patients in whom surgery is not feasible, CAS can be considered as an effective alternative. Further studies on patient characteristics might indicate additional patient groups in the nearby future that will be better off with CAS.

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